PROTOCOL TITLE: Bacteriostatic Normal Saline versus lidocaine for intradermal anesthesia during lumbar medial branch block

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EXTERNAL (NON-EMORY) COLLABORATORS N/A ☐: N/A)

VERSION: 1.1 – 06/06/2020.

FUNDING SOURCE: Funding will be supplied internally from the Pain Medicine Fellowship academic funds. No grants or external funding has been obtained. .

REVISION HISTORY

Revision #	Version Date	Summary of Changes
1.0	04/14/2020	Initial protocol
1.1	06/06/2020	Changes requested by IRB

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1.0 Study Summary

Study Title	*Bacteriostatic Normal Saline versus lidocaine for intradermal anesthesia during lumbar medial branch blocks*
Study Design	Randomized, double blinded, comparative study
Primary Objective	To determine if intradermal administration of bacteriostatic normal saline is less painful than 1% lidocaine plain
Secondary Objective(s)	To determine if intradermal bacteriostatic normal saline provides a similar level of skin anesthesia compared to 1% lidocaine plain
Research Intervention(s)/Interactions	Creation of skin wheals during a chronic pain procedure, specifically lumbar medial branch blocks, and assessment of pain scores
Study Population	Chronic pain patients
Sample Size	40
Study Duration for individual participants	30 minutes
Study Specific Abbreviations/ Definitions	BNS – Bacteriostatic normal saline MBB – Medial branch block NRS – Numeric rating scale
Funding Source (if any)	Internal funds from the Pain Medicine Fellowship, Department of Anesthesiology, Emory School of Medicine

2.0 Objectives

2.1 The aim of this study is to test whether intradermal bacteriostatic normal saline reduces procedure-related pain compared to lidocaine 1% plain in subjects with chronic axial low back pain. Specifically, this study will compare the pain associated with creation of a skin wheal and the resulting level of anesthesia between the two medications during a lumbar medial branch block (MBB).

- Objective #1 – To compare the pain experienced with creation of a skin wheal with bacteriostatic normal saline versus 1% lidocaine plain.
- Objective #2 – To compare the pain experienced when placing a needle through the skin wheal created with bacteriostatic normal saline versus 1% lidocaine plain.

2.2 Hypotheses

- Hypothesis #1 – *Injection of bacteriostatic normal saline (BNS) for skin wheal will show lower patient-reported pain scores on injection than that of 1% lidocaine.*
- Hypothesis #2 – *Injection of BNS for skin wheal anesthesia is non-inferior to that of the injection of the standard of care, 1% lidocaine, during medial branch block procedure.*

3.0 Background

3.1 Interventional pain procedures are performed to aid in the diagnosis and treatment of chronic pain. Like any invasive procedure, they carry a risk of procedure-related pain that may affect the patient in a negative way. Temporary consequences include the heightened pain itself, anxiety, premature abortion of the procedure, increased heart rate and blood pressure, and vasovagal reactions. Longer-term issues include aversion and/or anxiety to future procedures. These procedures are performed in patients with chronic pain and they may experience a heightened level of pain compared to patients without chronic pain. Also, it is often the case that creation of a skin wheal with local anesthetic is the most painful part of the procedure. [1] Some clinicians have resorted to moderate sedation and even general anesthesia to help reduce procedure-related pain; however, recent guidelines have advised against this practice since it has been associated with negative outcomes. [2]

3.2 Lumbar medial branch blocks are a specific interventional pain procedure used to determine if chronic axial low back pain is originating from facet, or zygapophyseal joints. Facet joints are innervated by medial branch nerves which arise from the dorsal ramus branch of spinal nerve roots. The procedure entails blocking the corresponding medial branch nerves for a given facet joint with a small amount of local anesthetic. If the patient has significant pain relief, there is a high likelihood that their pain is arising from the targeted joints. [3,4] Because the procedure is diagnostic in nature, limiting the amount of local anesthetic injected is of paramount importance. If other possible pain-generating structures are blocked with local anesthetic, it will make it impossible to determine which structure is causing pain. Therefore, typically only a skin wheal is created to limit pain on needle insertion besides the local anesthetic injected at the medial branch nerve. It is also important to minimize intravenous sedation for the same reason. In addition to the consequences of increased procedure-related pain stated above, increased pain during a medial branch block has been show to increase false-negative results. [5]

3.3 A number of factors have been identified that affect the pain from intradermal injections (injectate, pH, size of needle, angle of needle, attitude/words of proceduralist).[6] Investigators have examined alternatives for a number of these factors including the addition of sodium bicarbonate[7] and smaller needle size[8]. Other studies have investigated alternatives to intradermal injections themselves including topical local anesthetics[9] and no local anesthetic at all[8,10]. Recently, a study was conducted that showed performing the medial branch block procedure without creating skin wheals may be less painful; however, the study used 25 gauge needles where in many cases a larger 22-gauge needle is used.[10] This study also re-demonstrated the painful nature of creating a skin wheal with lidocaine 1%.

3.4 There has been a significant amount of research on a specific alternative to local anesthetics - bacteriostatic normal saline (BNS), which contains 0.9% benzyl alcohol.[7,11-15] Benzyl alcohol is an opium alkaloid that is sometimes added to physiologic normal saline for its bacteriostatic properties.[11,16] It has been shown to be safe[17] with one case report of allergic dermatitis[16]. The anesthetic properties of benzyl alcohol have been known since 1918[18] although its structure differs from other local anesthetics making it unlikely to cause an allergic reaction in patients with a local anesthetic allergy[19].

3.5 There are studies showing bacteriostatic normal saline to be less painful on injection and also providing the same level of anesthesia compared to lidocaine.[7,12-14] However, to our knowledge, no studies have been conducted comparing BNS to lidocaine for interventional pain procedures in a chronic pain population.

4.0 Study Endpoints *

4.1 The primary study endpoint is the improvement in procedure-related discomfort during a lumbar MBB.

4.2 There are no safety-related endpoints.

5.0 Study Intervention/Investigational Agent

5.1 The study intervention is the creation of a skin wheal (intradermal injection) with BNS and 1% lidocaine plain.

5.2 Drug/Device Handling: The storage, handling, and blinding of the medications will be performed by Grady Pharmacy using their established protocol. The administration of the medications (i.e. intradermal injection) will be performed by the principal investigator (PI).

6.0 Procedures Involved*

6.1 An individual's participation will occur during a lumbar medial branch block procedure. All subjects will have qualified for a lumbar medial branch block due to axial low back pain with lumbar spondylosis as the primary diagnosis. All subjects would have received lumbar medial branch blocks during their normal clinical course whether or not they choose to participate in this study

6.2 This study will focus solely on skin wheal creation and resulting skin anesthesia with lidocaine 1% and bacteriostatic saline. The lumbar medial branch block procedure typically requires two or more skin wheal injections prior to placement of the spinal needle that ultimately delivers the block. Subjects will serve as their own control. The first two skin wheals will be utilized for the study and the medications will be randomized with both the subject and investigator blinded to the medication used for each one. The first two skin wheals and placement of the first two spinal needles through these skin wheals will be performed by the principal investigator to promote consistency.

6.3 Using a standardized script, the participant will be informed that the medication will be administered. The skin wheal will be created by injecting the medication intra-dermally with a 26 gauge needle. The patient will be asked to rate on the numerical rating scale (NRS) the pain experienced with creation of the skin wheal. This process will then be repeated with the second skin wheal. Next, the first needle for the block will be inserted through the first skin wheal. The patient will again be asked to rate, on the NRS, the pain of needle insertion. For this procedure, a 22 gauge Quincke spinal needle will be used with a length of either 3.5 or 5 inches. This process will again be repeated by inserting the second needle through the second skin wheal.

6.4 At this point, the individual's participation in the research study is complete and the lumbar medial branch block will be continued as usual with any subsequent skin wheals created with 1% lidocaine plain (standard of care, not study related). The remainder of the medial branch block (after the conclusion of the individual's participation in the study) may be performed by the pain fellow or the principal investigator (attending).

6.5 Basic demographics (age, gender) and baseline pain score will be collected directly from the participant by the investigator before the intervention. During and after the intervention, the levels (L2, L3, L4, etc) and laterality injected and pain scores from the intervention will be collected directly from the subject by the investigator. No identifiable PHI will be collected or stored.

7.0 Data and Specimen Banking* N/A ☐

N/A

8.0 Sharing of Results with Participants*

8.1 This study does not involve any testing (diagnostic, genetic, imaging, etc.) that may generate potentially shareable results.

9.0 Study Timelines*

9.1 The duration of an individual participant's participation is approximately thirty (30) minutes. We anticipate the duration of enrollment to be approximately four (4) months assuming an average of three to four (3-4) lumbar medial branch blocks scheduled per week based on past procedure volumes. We anticipate an additional one (1) month for data analysis.

10.0 Inclusion and Exclusion Criteria*

10.1 When the patient arrives for the scheduled lumbar medial branch block, the subject will be consented for the procedure. After consenting for the procedure, one of the investigators will screen the patient for eligibility in the study.

10.2 Inclusion criteria – any patient scheduled for an initial lumbar medial branch block

10.3 Exclusion criteria

- Allergy to local anesthetics
- Fibromyalgia
- Inability to provide informed consent in English

10.4 We will also exclude the following special populations:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

10.5 Community Participation: N/A

11.0 Vulnerable Populations* N/A ☐

N/A

12.0 Local Number of Participants

12.1 Based on the power analysis, the total number of participants will be forty (40). We will plan to screen fifty (50) subjects assuming some may not consent to the study or may be excluded based on the exclusion criteria. Since the lumbar medial branch block is rarely performed in patients with a local anesthetic allergy or fibromyalgia, we expect the excluded subjects to be quite low.

13.0 Recruitment Methods

13.1 Potential participants will be asked to participate after he/she has consented to the lumbar medial branch block procedure.

13.2 Participants come from the patient population at the Grady Pain Clinic.

13.3 Any patient that is planning to undergo a lumbar medial branch block is a potential participant.

13.4 There will not be any recruitment materials since only patients undergoing lumbar medial branch blocks are potential participants which is a small subset of the patient population at the Grady Pain Clinic.

13.5 There will be no payments for participation or reimbursement for expenses/travel since the overall procedure is part of the subject's usual medical care

14.0 Withdrawal of Participants*

14.1 If a participant choses to not undergo the procedure after consenting but before creation of the first skin wheal, the participant will be withdrawn from the research.

14.2 If a participant choses to abort the procedure after creating of the first skin wheal, the procedure will be immediately stopped. While this participant will not count to our goal of forty (40) participants, the data will be analyzed to identify if there is a pattern regarding subjects that abort the procedure (i.e. is the creation of the skin wheal too painful or does not supply an adequate level of anesthesia for the spinal needle).

15.0 Risks to Participants*

15.1 It is foreseeable that the participant may experience pain/discomfort with the creation of the skin wheal or placement of the spinal needle through the skin wheal created by BNS. Since creation of a skin wheal with 1% lidocaine plain is standard of care, pain/discomfort occurring from this is unfortunately expected and unavoidable and the basis of performing this research to identify better options. The probability that the participant will experience significantly more pain/discomfort from BNS is very low given the results of prior studies. Any pain/discomfort experienced related to the skin wheal will be of a very short duration (seconds).

15.2 The participant may experience an allergic reaction to the medications however this is also extremely low.

15.3 Given the short duration of the medications administered, there are no risks to an embryo or fetus should the subject become pregnant after the study. Subjects currently pregnant are excluded.

16.0 Potential Benefits to Participants*

16.1 A potential benefit includes less pain with injection of BNS; however, the magnitude of this benefit is low since only one skin wheal will be created with BNS. The rest will be created with 1% lidocaine plain.

17.0 Data Management* and Confidentiality

17.1 Data will be analyzed using SAS 9.4 (Cary, NC) by the Anesthesiology Department's Biostatistician. For the first hypothesis, a General Linear Model will be applied, which is equivalent to a modified matched-pairs t-test, but allows for inclusion of potential confounders, such as the injection order. If assumptions of the General Linear Model are not met, e.g. the data are too leptokurtic or too positively skewed, then another statistical test such as Ordinal Logistic Regression will be used instead. For the second hypothesis, a non-inferiority test will be conducted, calculating delta as the maximum value for the 90% confidence interval, with an effect size of 0.24, an alpha set at 0.1, and a standard deviation of the difference determined from the sample data.

17.2 Power analysis was conducted with G*Power 3.1.9.4 (Düsseldorf, Germany). [20] A two-tailed a priori difference between two dependent means (matched pairs) was conducted. Alpha (Type I error) was set at 0.05 and power was set at 0.80. An effect size was set at 0.46, which is the mean effect size of a meta-analysis, [15] and is lower than the effect size of 0.52 calculated for a similar study. [11] This yielded a minimum required sample size of N=40.

17.3 Guidelines provided by the Grady/Emory Data and Safety Monitoring Board will be followed for this study data. Envelopes with random assignment of subjects to treatment arms will be in a locked filing folder and stored at the Grady Pain clinic office. No names, MRNs, or other personal identifiers will be used for the subjects - they will be given a random number identifier. Data results of subject's VAS scores will be immediately loaded to an encrypted and password protected Excel file and/or RedCap. The principal and secondary investigators will have access to the locked office/filing folder. If any reportable events are identified, they will be reported to the IRB as required by regulations. All study records will be reviewed at least annually.

17.4 Data results of subject's NRS scores will be immediately loaded to an encrypted and password protected Excel file and/or RedCap. The data will include the randomly assigned number identifier of the subject and the result of their NRS score. Data will be stored for 3 years. Only Brian

Bobzien, MD (PI) will have access to the data, and he is responsible for the receipt and transmission of the data.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants*

18.1 Due to the nature of the study using products that are currently commercially available and FDA approved for injection, it is unlikely that there would be major untoward events that are novel. The most likely possible event would be an unexpected allergic reaction to either lidocaine 1% or bacteriostatic saline, which would be identified at the time of the procedure. The secondary safety data being reviewed would be patient's ability to tolerate injection of or needle insertion with both the lidocaine 1% and bacteriostatic saline. During the study, the safety data will be monitored by the fellow on rotation at Grady along with Dr. Bobzien (PI). The fellow on rotation will monitor safety data via case report forms completed on each procedure detailing the procedure and any complications. Safety data collection will be a continuous process via case report forms starting at the beginning of data collection. Safety data will be reviewed on a monthly basis by the fellow on their Grady rotation. If either a high rate of unexpected allergic reactions or inability of patients to tolerate injection of or needle insertion with both the lidocaine 1% and bacteriostatic saline is identified then this would trigger suspension of the research. Efficacy data will be reviewed on a quarterly basis by the six fellows and Dr. Bobzien (PI).

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Patients will only be interacting with providers who would otherwise be participating in their care regardless of participation in the study. Participation in the study will not introduce any additional persons interacting with the patients.

19.2 The questions being asked will be standardized and will only be evaluating a patient's level of pain during an examination or procedure they would otherwise be receiving regardless of their participation in the study. No additional examinations or procedures will be asked of the patient's that they would not otherwise receive due to their diagnosis or plan of care.

19.3 The research team, consisting of the current pain fellows and Dr. Bobzien (PI), will access patient information via the Epic EEMR system at Grady Memorial Hospital. No information other than that would otherwise be available in order to routinely treat patients will be made available.

20.0 Economic Burden to Participants

20.1 Participants will not incur any costs related to participation in this study.

21.0 Consent Process

21.1 Consent will be obtained from participants in person the day of the procedure. This will be performed in an exam room prior to taking the patient to the procedure room. Consent will be obtained by an investigator. All researchers will be educated on the patients and procedure that this study is applicable towards in order to ensure the consistent consenting process of applicable patients. No waiver for any elements of the consent or HIPAA authorization will be needed. The therapeutic/diagnostic procedure performed on the patient will be unchanged, only the solution injected for skin topicalization will be randomized therefore no changes to the procedure consent form must be made. No vulnerable groups (children, prisoners, pregnant women, cognitive impairment, and employees) will be included in the study. The risk of coercion or undue influence in enrolling patients in this study is low. However all individuals obtaining consent will be educated on ethical practice and the voluntary nature of patient participation in this research study. Comprehension of the informed consent will be ensured by providing both verbal and written detailed information to the patient. The patient will also be asked if they have any questions, and if so ample time will be allowed for clarification.

Non-English-Speaking Participants N/A ☐ N/A

Participants who are not yet adults (infants, children, teenagers) N/A ☐ N/A

Cognitively Impaired Adults N/A ☐ N/A

Adults Unable to Consent N/A ☐ N/A

22.0 Process to Document Consent in Writing

22.1 Consent will be documented in writing by having the participant sign the consent document. A copy will be provided to the participant and the original document will be stored in a locked cabinet in a locked office in the clinic.

22.2 Consent document attached.

23.0 Setting

23.1 The research study will be conducted at the Grady Pain Clinic which is located on the first floor of Grady Memorial Hospital in area 1A. Identification, screening, consent, and procedures will all be conducted in this clinic.

24.0 Resources Available

24.1 The Grady Pain Clinic is located on the first floor (1A) of Grady Memorial Hospital. It has 4 exam rooms, 1 procedure/fluoroscopy room, and 1 recovery room. There is one LPN at this time with positions for one RN and one CMA outstanding. The clinic sees over 300 patients a month with the majority of those patients having chronic low back pain. A lumbar medial branch block is a diagnostic/prognostic procedure performed to identify back pain from lumbar facet joints and likely response to radiofrequency ablation of the medial branch nerves. From examining past procedure volume, this procedure is performed three to four (3-4) times a week on average. We anticipate fifty (50) potential participants over the four (4) months window and expect enrollment of 80% or forty (40) participants.

24.2 This research is being performed as part of the Pain Medicine Fellowship research/quality improvement project. The principal investigator, Dr. Brian Bobzien, MD, is Director of the Grady Pain Clinic and works full-time at the clinic. Pain Medicine fellows rotate through the clinic on a monthly basis and will participate in research study as co-investigators. We anticipate an additional thirty (30) minutes to complete the screening, consent, and study intervention. The principal investigator will devote four to five (4-5) hours per week to conducting and completing the research.

24.3 The nursing staff will be informed about the protocol prior to initiating enrollment; however, nursing staff will not be directly involved in aspects of the research, just the investigators. The co-investigators meet on a monthly basis currently and will continue until the study is completed.

24.4 As mentioned earlier, the risk of pain/discomfort with this research study will be short-lived. In the event of an allergic reaction, although unlikely, the patient will be managed supportively in the Pain Clinic similarly to any other patient that may experience an allergic reaction during a procedure and will be referred to the Grady's Allergy clinic. If the patient reports psychological issues related to their participation in this study, the patient will be referred to Grady's mental health department at 10 Park Place.

25.0 Multi-Site Research when Emory is the Lead Site*N/A ☐

25.1 N/A

26.0 References

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